REMARKS/ARGUMENTS

The foregoing amendments to the specification confirm that all deposits were made under the terms of the Budapest Treaty, and meet the criteria set forth in 37 C.F.R. §§1.801-1.809. The amendments to the claims have been necessitated by a restriction requirement, or serve to correct errors of formal nature. All amendments were made without prejudice, are fully supported by the specification as originally filed, and do not add new matter. Applicants specifically reserve the right to pursue any subject matter not covered by the claims as currently amended in one or more continuing applications.

Applicants note the finality of the restriction requirement originally communicated in the Office Action mailed on August 26, 2005. As a result, prior to the present amendments Claims 1-46 were pending in this application, of which Claims 1-13, 15-19, and 29-32 were under examination, while Claims 14, 20-28, and 33-46 were withdrawn from consideration. Claims 1, 15, 16, and 32 have been amended, Claims 4-7, 18-31, and 33-46 have been canceled by the present amendment. The claims reciting the administration of a second therapeutic agent are examined to the extent that the agent is an immunosuppressive agent, and the claims reciting conjugated antibodies are examined to the extent that the antibody is not conjugated to a cytotoxic agent. However, since the latter limitations result from an election of species requirement, upon the allowance of a generic claim, Applicants will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 C.F.R. §1.141.

Rejections Under 35 U.S.C. §112, First Paragraph – Enablement

Claims 1-13, 15-19, and 29-32 have been rejected as allegedly failing comply with the enablement requirement of 35 U.S.C. §112, first paragraph. Claims 4-7 and 18-31 have been canceled, which moots their rejection. The rejection of the remaining claims is respectfully traversed.

According to the rejection, "the antibody 2C4 produced by hybridoma cell line deposited under ATCC Deposit No. HB-12697 recited in Claims 3, 9, and 31 are [sic] required to practice the claimed invention." The Examiner notes that Applicants should provide assurances that the deposit was made under the terms of the Budapest Treaty and meets the criteria set forth in

37 C.F.R. §§1.801-1.809. The specification has been amended to provide these specific assurances, which are further confirmed herein. Accordingly, this reason for the rejection is moot.

A further reason named in support of the rejection is that, according to the Examiner, "the specification does not teach how to treat any and all 'non-malignant disease' or 'disorder' involving abnormal activation of any ErbB receptor or any ErbB ligand, any disorder involved in abnormal activation of EGFR . . . " Without acquiescing to the rejection or the Examiner's reasoning underlying the rejection, the claims have been amended to recite "psoriasis" as the disease to be treated, which obviates this ground of rejection.

Finally, the Examiner asserts that the specification does not provide enablement for the use of any monoclonal antibody to ErbB2, or any humanized 2C4 antibody alone or in combination with any immunosuppressive agent. The Examiner acknowledges that the specification teaches various monoclonal antibodies that bind specifically to human ErbB2, such as 7C2, 7F3, 4D5, and 2C4, discloses humanized antibodies and their binding fragments, teaches that 2C4 and similar antibodies inhibit the association of ErbB2 and ErbB3 in certain mammary tumor cell lines, and that the binding of 2C4 to human ErbB2 blocks EGF-, TGFα- or HRG-mediated activation of MAPK kinase in MCF7 cancer cells. However, in support of the rejection, the Examiner asserts that there is "no evidence of record that non-malignant disease or disorder such as psoriasis may be treated with any ErbB2 antibody," and adds that the "specification fails to teach an in vitro assay that is predictive of success in vivo of treating all 'non-malignant disease or disorder [sic]." From this, the Examiner concludes that "one skilled in the art would have reason to doubt that any anti-erbB2 antibody administered in any manner would be able to treat all non-malignant diseases or disorders, any disorder such as psoriasis."

The Examiner cites Sauder *et al.*, J Cutan Med Surg 8(4):205-212 (2004) as allegedly teaching that psoriasis is a T-cell mediated inflammatory skin disease, and that there is no cure for psoriasis. Sauder *et al.* is further relied on for its teaching that traditional options for treating psoriasis involve the use of both topical and systemic medications.

Giaccone *et al.*, Annals of Oncology 16:538-548 (2005) is cited as allegedly teaching that predicting the future of patients using EGF receptor targeted agents is unpredictable, and that

further research is required to determine the optimal dosing strategy for HER1/EGFR tyrosine kinase inhibitors.

Puddicombe *et al.*, J. Biochemistry 271(48):30392-30397 (1996) is relied on for its alleged teaching that the interaction of epidermal growth factor/transforming growth factor alpha chimera with human epidermal growth factor receptor reveals unexpected complexities, and the properties of the ligand are not always predictable.

Finally, the Examiner notes that there is "insufficient guidance" as to how to make and use any IL-1 antagonist, any TNF-antagonist, or any ErbB antagonist.

The rejections, as they related to the pending claims, are vigorously traversed.

All claims currently pending relate to the treatment of psoriasis in a mammal, such as a human, by administration of a therapeutically effective amount of an antibody which binds ErbB2. The claims do not refer to other ErbB receptors, therefore, all comments and references concerning EGFR or other ErbB receptors are irrelevant to the issue of enablement for the current claims. The only question is whether the treatment of psoriasis with an ErbB2 antibody is enabled. Applicants submit that it is.

When making a rejection on the ground of alleged lack of enablement, the Examiner has the "initial burden of setting forth a reasonable explanation as to why [he/she] believes that the scope of protection provided by [the] claim is not adequately enabled by the description of the invention provided in the specification." *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). Without a reason to doubt the truth of the statements made in the patent application, the application must be considered enabling. *In re Wright, supra*; *In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971).

The test for enablement entails an analysis of whether one skilled in the art would have been able at the effective filing date to practice the invention using information disclosed in the application and information known in the art without undue or unreasonable experimentation (MPEP § 2164.01; see In *re Wands,* 858 F.2d 731, 8 USPQ 2d 1400, [Fed. Cir. 1988]). A finding of lack of enablement and determination that undue experimentation is necessary requires an analysis of a variety of factors *(i.e.,* the *In re Wands* factors). The most important factors that must be considered in this case include: 1) the nature of the invention; 2) the level of

ordinary skill in the art; 3) guidance provided in the specification; and 4) the state of the prior art. "[H]ow a teaching is set forth, by specific example or broad terminology, is not important"; and furthermore still, "limitations and examples in the specification do not generally limit what is covered by the claims" (MPEP § 2164.08). The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. *Ansul Co. v. Uniroyal, Inc.* 448 F.2d 872, 878-79; 169 USPQ 759, 762 63 (2d Cir. 197 1), cert. Denied, 404 U.S. 10 18, 30 L. Ed. 2d 666, 92 S. Ct. 680 (1972). The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. The legal standard merely requires that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. *Enzo Biochem., Inc. v. Calgene, Inc.,* 188 F.3d 13 62 (Fed. Circ. 1999), at 1372 (quoting *In re* Vaeck, 947 F.2d 488, 496 (Fed. Cir. 1991)).

As stated above, the invention claimed in the present application concerns the treatment of psoriasis using ErbB2 antibodies. As required by case law (see, *e.g., In re Wright, supra*; and *In re Marzocchi, supra*), the Examiner must provide reasons to doubt the truth of the statements made in a patent application. Applicants submit that valid reasons to doubt the truth of the statement that psoriasis can be treated with ErbB2 antibodies have not been provided, therefore, the disclosure must be accepted as enabling.

Treatment of psoriasis

Of the citations relied on in support of the present rejection, Sauder *et al.* is the only reference that addresses the treatment of psoriasis. The Examiner cites Sauder *et al.* in support of the notion that there is no cure for psoriasis. While this might be the case, the question whether a cure exists or not is irrelevant to the issue of enablement for the claimed invention. The claims are not directed to a cure of psoriasis. The claims are directed to a treatment of psoriasis. It is understood by those skilled in the are that "cure" means restoring a patient to

health, so that the disease treated does not recur. In contrast, "treatment" allows for a wide range of possibilities, including alleviating the symptoms or improving the condition of a disease, without completely eliminating the disease. Sauder *et al.* are fully aware of this distinction, when stating: *"No cure for psoriasis has been found, but many therapies are available to treat the disease."* (Page 206, second column, lines 7-8; emphasis added.) The Examiner cited the first half of this sentence in an attempt to support the rejection. In fact, the complete sentence supports Applicants' position that at the time the present invention was made there were various therapeutic approaches available for the treatment of psoriasis, therefore, one of ordinary skill at the relevant time would have reasonably accepted the teaching of the present application about a further treatment. This is particularly true, since the level of ordinary skill in the art of medicine, antibody technology and protein-based drugs is known to be high, represented by a Ph.D. scientists or an M.D. with several years of experience. The fact that psoriasis responds to various treatment is also clearly communicated in the specification, which states: *"There is no known cure, however, psoriasis patients have successfully responded to treatment with various immunomodulatory or immunosuppressive agents, e.g., cyclosporin, tacrolimus (FK506), and DAB389 IL2, which selectively target activated T-cells."* (Page 52, lines 36-38.)

Use of antibodies which bind ErbB2 to treat psoriasis

Sauder et al. discuss antibodies and antibody-like molecules that have been shown some activity in the treatment of psoriasis. These include a humanized CD11a monoclonal antibody (efalizumab), a human fusion protein composed of the Fc portion of human IgG and the binding site of lymphocyte function-associated antigen-3 (LFA-3) (alefacept), a dimeric fusion protein of soluble TNF receptor and the Fc portion of human IgG (etanercept) and a chimeric monoclonal TNF antibody (iniximab). Antibodies which bind ErbB2 were well known in the art at the priority date of the present application, and are discussed, at great length, in the specification, such as, for example, at page 2, lines 10-37; page 11, lines 34-37; page 12, line 9 – page 15, line 7; page 22 line 35 – page 43, line 38, the Examples, and the references cited therein. This disclosure includes a detailed description of the structure, function, preparation and use of antibodies which bind ErbB2, and clearly enables one of ordinary skill to make and use such antibodies. This is particularly true since a particular ErbB2 antibody, HERCEPTIN®

(trastuzumab) is commercially available. Indeed, the Examiner has acknowledged that the specification teaches various monoclonal antibodies that bind specifically to human ErbB2, such as 7C2, 7F3, 4D5, and 2C4, discloses humanized antibodies and their binding fragments.

In view of the fact that psoriasis is not a disease which is inherently "untreatable," and in view of the extensive knowledge in the art and teaching provided in the specification about ErbB2 antibodies, the Examiner is required to name specific reasons why one or ordinary skill would doubt that that ErbB2 antibodies can be used to treat psoriasis, or could not use such antibodies, without undue experimentation. The rejection gives the following specific reasons: (1) there are no examples supporting the treatment of psoriasis with ErbB2 antibodies; (2) there is no evidence of record that a non-malignant disorder, such as psoriasis, can be treated with ErbB2 antibodies; (3) there is no evidence of record that ErbB2 is present in karatinocytes; and (4) neither the specification nor the art teaches that breast cancer cell lines are an appropriate model for psoriasis.

As to the first reason, there is no requirement in patent law to support the claims by working examples. How a teaching is set forth, by specific example or broad terminology, is not important. Nonetheless, the specification contains a specific example (Example 4) teaching the use of ErbB2 antibodies, such as rhuMAb 2C4 or humanized 7F3 to treat psoriasis. The example includes dosage ranges and dosing regimens, and provides methods for assessing the efficacy of treatment. Based on this treatment, one of ordinary skill would know how to treat psoriasis with ErbB2 antibodies, without undue experimentation.

As to the second and third reasons, it was known in the art at the time the present invention was made that ErbB receptors, including ErbB2 are expressed by keratinocytes. See, for example, De Potter et al., Exp Cell Res. 271(2):315-28 (2001), a copy of which is submitted with the attached Supplemental Information Disclosure Statement.

As to the fourth reason, Applicants do not assert that breast cancer cell lines are an appropriate model to treat psoriasis, rather provide specific teaching for the treatment of psoriasis with ErbB2 antibodies, which teaching would be viewed as credible by those skilled in the art in view of the extensive teaching about ErbB2 antibodies, as discussed above, and the knowledge that ErbB2 is expressed by keratinocytes. The teaching of the present application has since been

further confirmed by the post-published paper by Piepkorn *et al.*, Arch Dermatol Res. 295(3):93-101 (2003) (copy enclosed), which reports that heregulin is undetectable in normal epidermis but is upregulated in psoriasis, and further that heregulin colocalizes with the EGFR and ErbB3 receptors in the granular layer of skin, and in a declining gradient from the granular zone to the basal layer.

In view of the foregoing arguments and evidence, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

Rejections Under 35 U.S.C. §112, First Paragraph – Written Description

Claims 1-13, 15-19 and 29-32 were rejected as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. Claims 4-7 and 18-31 have been canceled, which moots their rejection. The rejection of the remaining claims is respectfully traversed.

In support of the rejection, as it applies to the amended claims, the Examiner states that the specification does not reasonably provide a written description of the binding specificity of all antibodies that bind any ErbB2. This statement is incorrect and is refuted by the Examiner's own acknowledgement that the specification discloses a series of antibodies binding ErbB2 along with their binding fragments. Such antibodies are not only described in the present application but have been deposited and are available from the ATTC, and their sequences have been described in published documents (incorporated by reference), well before the priority date of the present application. From the statement that there is "inadequate written description about the binding specificity of all antibody [sic]" (Page 7 of the Office Action), it appears that the Examiner believes that the disclosure of the binding specificity of every single antibody within the genus of antibodies binding ErbB2 would be required to meet to written description requirement for the genus. This is clearly not the proper legal standard.

In Regents of the University of California v. Eli Lilly, 119 F.3d 1559, 1566, 43 USPQ2d 1398, 1404 (Fed. Cir. 1997), the Federal Circuit held that an adequate written description of genetic material "requires a precise definition, such as by structure, formula, chemical name, or physical properties." A description of a genus of cDNAs may be achieved by means of a

recitation of a representative number of cDNAs, defined by nucleotide sequences, falling within the scope of the genus or a recitation of structural features to the members of the genus, which features constitute a substantial portion of the genus. *Id.* 119 F.3d at 1569, 43 USPQ2d at 1406. The Guidelines for Examination of Patent Applications Under the 35 U.S.C. §112, & 1, 'Written Description' Requirement, 66 F.R. 1099, 1106 (January 5, 2001) (hereinafter "Written Description Guidelines") provide that applicant may show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that Applicant was in possession of the claimed invention, *i.e.,* complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. Written Description Guidelines at 1106. By providing the sequences of a representative number of antibodies coupled with the requirement that they bind ErbB2, Applicants have met this requirement. Based on this description, one of ordinary skill would reasonably accept that applications were in the possession of the genus of ErbB2 antibodies used in the methods of the present invention at the time the present invention was made.

Since the "non-malignant disease" is now specified as "psoriasis," Applicants do not claim a genus of non-malignant diseases, and the species of psoriasis is adequately described throughout the specification, such as, for example, at page 17, lines 4-8; page 39, line 33 – page 43, line 38, and in Example 5.

The Examiner's assertions that there is no adequate written description for the immunosuppressive agents which might be optionally administered to supplement the ErbB2 antibody treatment is believed to be misplaced. Applicants have shown that there is adequate written description for the invention, which is the use of ErbB2 antibodies to treat psoriasis. Applicants are not legally required to prove that features recited in claims dependent from generic claims reciting the broadest aspect of the invention, carrying its recitations, independently meet various conditions of patentability, including the written description requirement. Furthermore, immunosuppressive agents are sufficiently described throughout the specification, such as, for example, at page 21, lines 12-32 of the specification.

In view of the foregoing arguments, the Examiner is respectfully requested to withdraw the present rejection.

Rejections Under 35 U.S.C. §102

Claims 1-8 and 16-18 have been rejected under 35 U.S.C. §102(b) as allegedly being anticipated by WO 01/15730, published on March 8, 2001. According to the rejection, WO 01/15730 teaches a method of treating non-malignant diseases or disorders involving abnormal activation or production of an ErbB receptor, such as benign hyperproliferative epithelial, inflammatory immunological disorders, by administration of an antibody which binds ErbB2, such as humanized 4D5, 7C2, 7F3, 3D5, and 2C4.

Claims 4-7 and 18 have been canceled, which moots their rejection. The rejection of the remaining claims is respectfully traversed.

In the rejection, the Examiner specifically refers to page 14, lines 9-14 and page 30, lines 31-38 of the cited PCT publication.

The PCT publication at page 14, lines 9-14 states: *"A 'disorder' is any condition that would benefit from treatment with the anti-ErbB2 antibody. This includes chronic and acute disorders or diseases including those pathological conditions which predispose the mammal to the disorder in question. Non-limiting example of disorders to be treated herein include benign and malignant tumors; leukemias and lymphoid malignancies; neuronal, glial, astrocytal, hypothalamic and other glandular, macrophagal, epithelial, stromal and blastocoelic disorders; and inflammatory, angiogenic and immunologic disorders."*

The PCT publication at page 30, lines 31-38 *lists "benign and malignant tumors (e.g. renal, liver, kidney, bladder, breast, gastric, ovarian, colorectal, prostate, pancreatic, lung, vulval, thyroid, hepatic carcinomas; sarcomas; glioblastomas; and various head and neck tumors); leukemias and lymphoid malignancies; other disorders such as neuronal, glial, astrocytal, hypothalamic and other glandular, macrophagal, epithelial, stromal and blastocoelic disorders; and inflammatory, angiogenic and immunologic disorders."*

Contrary to the Examiner's assertion, "benign hyperproliferative epithelial" diseases are not listed, nor is psoriasis mentioned.

To anticipate a claim, a prior art reference must disclose every limitation of the claimed invention, either explicitly or inherently. See Glaxo Inc. v. Novopharm Ltd., 52 F.3d 1043, 1047, 34 USPQ2d 1565, 1567 (Fed. Cir. 1995). Anticipation is an issue of fact, see In re Graves, 69 F.3d 1147, 1141, 36 USPQ2d 1697, 1700 (Fed. Cir. 1995); Diversitech Corp. v. Century Steps, Inc., 850 F.2d 675, 677, 7 USPQ2d 1315, 1317 (Fed. Cir. 1988), and the question whether a claim limitation is inherent in a prior art reference is a factual issue on which evidence may be introduced, see Continental Can Co. USA v. Monsanto Co., 948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991).

In the present case, the use of ErbB2 antibodies to treat psoriasis is not explicitly disclosed in WO 01/15730. Nor does WO 01/15730 inherently disclose the treatment of psoriasis with antibodies which bind ErbB2.

It is well established that an inherent feature or result disclosed in a prior art reference, in order to be anticipatory, must be *consistent, necessary, and inevitable*, not merely possible or probable. Thus, in Hansgirg v Kimmer, 102 F.2d 212; 40 USPQ (CCPA 1939), the CAFC's predecessor held: "*Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.*" A limitation or the entire invention is inherent and in the public domain if it is the "natural result flowing from" the explicit disclosure of the prior art. Eli Lilly v. Barr Labs., 251 F.3d 955, 970 (CAFC 2001); In re Kratz, 592 F.2d 1169, 1174 (CCPA 1979). See also, Continental Can Co. v. Monsanto Co., 948 F.2d 1264, 1268 (Fed. Cir. 1991) for the holding that a prior art reference may anticipate without disclosing a feature of the claimed invention if the missing characteristic is "necessarily present" in a single anticipating reference. Thus, the requirements of inherent anticipation are met only, if a person of ordinary skill in the art, presented with all facts, would understand that the missing element or feature is always necessarily present.

In view of the complexity of the pathogenesis of psoriasis, based on the mention of treating inflammatory or immunologic disorders with ErbB2 antibodies, one of ordinary skill would not conclude that psoriasis can be necessarily and inevitably treated with such antibodies. Accordingly, the reconsideration and withdrawal of the present rejection is respectfully requested.

Rejections Under 35 U.S.C. §103(a)

(1) Claims 1, 19 and 29-31 were rejected under 35 U.S.C. §1039a) as allegedly obvious over WO 01/15730 in view of WO 98/02540 (published January 22, 1998). WO 01/15730 has been applied as in the previous rejection. The Examiner notes that the claimed invention differs from the teachings of the reference only when the disease treated is psoriasis. WO 98/02540 has been cited for its alleged teaching of treating psoriasis by administering to a mammal various heteromultimeric ErbB-Ig adhesions, comprising the extracellular domain of ErbB2-IgG. According to the rejection, "it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the heteromultimeric adhesions ErbG [ErbB]-Ig for treating psoriasis as taught by WO 98/02540 publication for the antibody that binds ErbB2 such as 2C4 or humanized 2C4 that blocks ligand activation of the ErbB4 receptor as taught by the WO 01/15730 publication." The Examiner further asserts that one of ordinary skill would have been motivated to combine the two references, because "antibody which binds ErbB2 is useful for treating non-malignant disease or disorder involving abnormal activation or production of ErbB2 receptor such as benign hyperproliferative epithelial, inflammatory angiogenic immunological disorders [sic] as taught by the WO 02/15730 publication."

Claims 19 and 29-31 have been canceled, which moots their rejection. The rejection of claim 1 is vigorously traversed.

Applicants submit that the Examiner failed to establish a *prima facie* case of obviousness for the invention claimed in the present application. In particular, the Examiner failed to provide a sufficient showing why a skilled person, confronted with the same problem as the present inventors and with no knowledge of the claimed invention, would have been motivated as of the effective filing date to select the elements from the cited prior art references for combination in the manner claimed in the present application. Applicants submit that, rather than applying the proper legal standard, the Examiner has engaged in impermissible hindsight reconstruction of the claimed invention, using the claimed invention as a road map to piece together the teachings of the cited prior art references to show that the claimed invention is rendered obvious.

The U.S. Court of Appeals for the Federal Circuit has held that:

> [t]he PTO has the burden under section 103 to establish a *prima facie* case of obviousness . . . It can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references. In re Fine, 837 F.2d 1071, 1074 (Fed. Cir. 1988).

The case law is also clear that the motivation to support a combination of references in a Section 103 rejection must withstand scrutiny.

In In re Rouffet, 149 F.3d 1350; 47 USPQ2d 1453 (Fed. Cir. 1998) , the CAFC reaffirmed that a suggestion to combine known elements present in various pieces of prior art is critical for establishing a *prima facie* case of obviousness. The CAFC observed that:

> [V]irtually all [inventions] are combinations of old elements." Environmental Designs, Ltd. V. Union Oil Co., 713 F.2d 693, 698, 218 U.S.P.Q. 865, 870 (Fed. Cir. 1983); see also Richdel, Inc. v. Sunspool Corp., 714 F.2s 1573, 1579-80, 219 U.S.P.Q. 8, 12 (Fed. Cir. 1983) ("Most, if not all, inventions are combinations and mostly of old elements."). Therefore, an examiner may often find every element of a claimed invention in the prior art. If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue. Furthermore, rejecting patents solely by finding prior art corollaries for the claimed elements would permit an examiner to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention. Such approach would be "an illogical and inappropriate process by which to determine patentability." Sensonics, Inc. v. Aerosonic Corp., 81 F.3d 1566, 1570, 38 U.S.P.Q.2d 1551, 1554 (Fed. Cir. 1996).
>
> In re Rouffet, 149 F.3d at 1357 47 U.S.P.Q.2d at 1457

The requirement that an Examiner must show a suggestion to combine references cited in support of an obviousness rejection is a critical safeguard against hindsight reconstruction of an invention. The motivation to modify a reference can come from: (1) the nature of the problem to be solved, (2) the teachings of the prior art itself, or (3) the knowledge of persons of ordinary skill in the art. In re Rouffet, 149 F.3d at 1358; 47 U.S.P.Q.2d at 1458.

In response to the previous rejection, Applicants have shown that the primary reference, WO 01/15730, does not teach, either explicitly or inherently, the treatment of psoriasis. The secondary reference, WO 98/02540, is cited for its teaching that ErbB-Ig chimeric heteromultimer immunoadhesins can be used to treat, among other things, "inflammatory,

angiogenic and immunologic disorders; psoriasis and scar tissue formation." (Page 25, line 8.) It is noteworthy that psoriasis is listed separately, and not as a species within an inflammatory, angiogenic, or immunologic disorder. This distinction further supports Applicants' position that psoriasis has acquired a separate place in the art, and thus, from the fact that certain inflammatory or immunologic disorders are described to respond to a treatment, it does not necessarily follow that psoriasis could be treated in a similar manner. In view of this distinction, one of ordinary skill in the art at the time the present invention was made would not have had any motivation to combine WO 01/15730 and WO 98/02540. Indeed, the only motivation to make the purported combination derives from the disclosure of the present application, and is the result of an impermissible hindsight reconstruction of the claimed invention.

Applicants further submit that even if WO 01/15730 and WO 98/02540 could be properly combined, they would still not make obvious the claimed invention. WO 01/157030 was cited for its teaching of the treatment of various non-malignant conditions, in particular inflammatory and immunologic conditions, using ErbB2 antibodies. WO 98/02540 teaches to use of heteromultimeric immunoadhesins, including the extracellular domains of two at least two different ErbB receptors (*e.g.*, ErbB2/ErbB3, ErbB2/ErbB4, ErbB3/ErbB4), to treat psoriasis. At the priority date of the present invention, based on these two disclosures, without the knowledge of the present invention, one of ordinary skill would not have concluded that antibodies, which bind ErbB2 could treat psoriasis with a reasonable expectation of success.

(2) Claims 15 and 32 have been rejected under 35 U.S.C. §102(a) as allegedly obvious over WO 01/15730 in view of WO 98/02540, as applied in the previous rejection, and further in view of Feldman *et al.* (Dermatol Online J. 6(1):4, 2000). The Examiner notes that Claims 15 and 32 differ from the combined teachings of the two PCT publications only in the additional administration of a second therapeutic agent, an immunosuppressive agent, which teaching is present in Feldman *et al.*

In response to the previous rejection, Applicants have shown that claim 1 is not rendered obvious by the combination of WO 01/15730 and WO 98/02540. Since Claims 15 and 32 depend from Claim 17, which depends from Claim 1, both of the rejected claims carry the

recitations of Claim 1 and are not obvious for the same reasons. Accordingly, the withdrawal of the present rejection would be in order.

All claims pending in this application are believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **P1979R1**).

Respectfully submitted,

Date: March 7, 2006

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